Phosphine-Catalyzed [3 + 2] Annulations of γ-Functionalized Butynoates and 1*C*,3*O*-Bisnucleophiles: Highly Selective Reagent-Controlled Pathways to Polysubstituted Furans
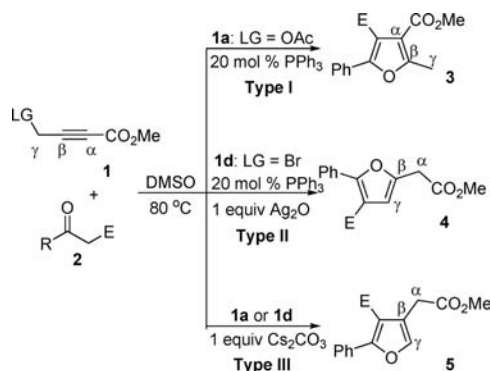
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ABSTRACT

In this paper, a reagent-controlled [3 + 2] annulation of γ-functionalized butynoates 1 and 1*C*,3*O*-bisnucleophiles 2 is reported, which leads to three distinct furan skeletons 3−5. A PPh₃ catalyst preferentially attached the β-position of 1a, facilitating α-addition to furnish Type I annulations. With the assistance of Ag₂O, Type II annulations were achieved via selective γ-substitution. In the absence of the PPh₃ catalyst, the reagent Cs₂CO₃ promoted β-addition to realize Type III annulations.

Polysubstituted furans represent an important class of five-membered heterocycles that appear widely in the structure of natural products,[1] therapeutic agents,[2] and fine chemicals.[3] Therefore, numerous protocols have been developed for the synthesis of polysubstituted furans.[4] Herein, we report a novel diversity-oriented strategy for furan synthesis based on the reactions of γ-functionalized butynoate **1** and **2** in a

(1) For representative furan-contained nature products, see: (a) Rodriguez, A. D. *Tetrahedron* **1995**, *51*, 4571. (b) Cimino, G.; Stefano, S. De.; Guerriero, A.; Minale, L. *Tetrahedron Lett.* **1975**, *14*, 1425. (c) Kupchan, S. M.; Shizuri, Y.; Shizuri.; Baxter, R. L.; Baxter.; Haynes, H. R. *J. Org. Chem.* **1977**, *42*, 348. (d) Zinsmeister, H. D.; Becker, H.; Eicher, T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 130. (e) Teles, H. L.; Hemerly, J. P.; Pauletti, P. M.; Pandolfi, J. R. C.; Araujo, A. R.; Valentini, S. R.; Claudia, M.; Youngd, M.; Bolzani, V. D. S.; Silva, D. H. S *Nat. Prod. Res.* **2005**, *19*, 319.

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(3) (a) Wong, H. N. C.; Yang, Y. *Tetrahedron.* **1994**, *50*, 9583. (b) Gabriele, B.; Salerno, G.; Lauria, E. *J. Org. Chem.* **1999**, *64*, 7687.

(4) For recent reviews, see: (a) Brown, R. C. D. *Angew. Chem., Int. Ed.* **2005**, *44*, 850. (b) Cacchi, S. *J. Organomet. Chem.* **1999**, *576*, 42. (c) Keay, B. A. *Chem. Soc. Rev.* **1999**, *28*, 209. (d) Hou, X. L.; Cheung, H. Y.; Hon, T. Y.; Kwan, P. L.; Lo, T. H.; Tong, S. Y.; Wong, H. N. C *Tetrahedron* **1998**, *54*, 1955. (e) Kirsch, S. F. *Org. Biomol. Chem.* **2006**, *4*, 2076.

(5) For reviews, see: (a) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535. (b) Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035. (c) Lu, X.; Du, Y.; Lu, C. *Pure Appl. Chem.* **2005**, *77*, 1985. (d) Nair, V.; Menon, R. S.; Sreekanth, A. R.; Abhilash, N.; Biju, A. T. *Acc. Chem. Res.* **2006**, *39*, 520. (e) Ye, L. W.; Zhou, J.; Tang, Y. *Chem. Soc. Rev.* **2008**, *37*, 1140. (f) Kwong, C. K.-W.; Fu, M. Y.; Lam, C. S.-L.; Toy, P. H. *Synthesis* **2008**, 2307.
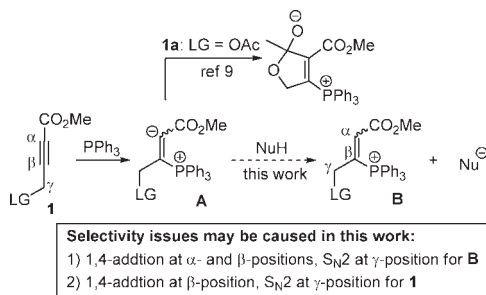
reagent-controlled manner, leading to three distinct molecular skeletons **3−5** (Scheme 1).

Scheme 1. Reagent-Controlled Synthesis of Furan Derivatives
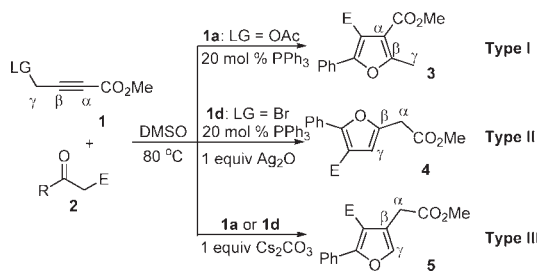
The phosphines (PR$_3$) have been remarkably effective catalysts for cycloadditions of electron-deficient C−C multibond systems.[5] Their basic success is derived from their strong nucleophilicity as a Lewis base for the formation of phosphinium-containing zwitterions via 1,4-addition of PR$_3$ to electron-deficient systems. While various electron-deficient systems, such as allenoates,[6] alkenes,[7] and alkynes,[8] have been well studied, relatively little attention has been focused on γ-functionalized butynoate **1**, and to date there has been only one report concerning this substrate (Scheme 2).

Scheme 2. Reactivity Profile of γ-Functionalized Butynoate **1**

Selectivity issues may be caused in this work:
1) 1,4-addtion at α- and β-positions, S$_N$2 at γ-position for **B**
2) 1,4-addtion at β-position, S$_N$2 at γ-position for **1**

In 2003, Krische and co-workers originally employed **1a** (LG = OAc) as starting material for convergent furan derivative synthesis with the use of an excessive PPh$_3$ reagent, in which the involved zwitterionic intermediate **A** is proposed to exhibit nucleophilicity to undergo intramolecular acyl-substitution (Scheme 2).[9] Encouraged by these results, we envisioned that the carbanion of **A** would also be capable of serving as a base to deprotonate pronucleophile, generating intermediate **B** with three contiguous electrophilic centers (α-, β-, and γ-position). Logically, every two of these three centers could attach with a 1,n-bisnucleophile to furnish a annulation process (Scheme 2). Moreover, butynoate **1** itself also bears two electrophilic centers available for nucleophilic attack, 1, 4 -addtion at the β-position, and S$_N$2-subtitution at the γ-position.[10] Therefore, one can imagine that the reaction between butynoate **1** and bisnucleophile would suffer from serious selectivity issues in the presence of a phosphine catalyst.

Because the aforementioned selectivity is likely to be a difficult challenge, we decided to pursue a more viable objective where compound **2a** was selected as 1C,3O-bisnucleophile to avoid the regioselectivity problem arising from a bisnucleophile partner. With these considerations in mind, we initiated our study by evaluating the reaction of **1a** and **2a** in DMSO at 80 °C with 20 mol % PPh$_3$ as a catalyst (Table 1, entry 1). To our delight, compound **3aa** was exclusively isolated in 91% yield. Thus, the PPh$_3$-catalyzed formal [3 + 2] annulation (Type I) of **1a** and **2a** was realized, in which both αC and βC of **1a** are incorporated into a furan product. Surprisingly, additional base was found to be nonessential for the reaction although byproduct HOAc was generated. Several bases, such as K$_2$CO$_3$, Na$_2$CO$_3$, Cs$_2$CO$_3$, and Ag$_2$O, have been tested and found not to impose any positive influence on the reaction, in terms of reaction rate and yield.

Table 1. Scope of Type I Annulations[a]

Entry	**1** (R^1)	**2** (R^2, E)	**3** (yield %)[b]
1	**1a** (H)	**2a** (Ph, CN)	**3aa** (91)
2	**1a** (H)	**2b** (4-MeO-C$_6$H$_4$, CN)	**3ab** (62)
3	**1a** (H)	**2c** (4-Br-C$_6$H$_4$, CN)	**3ac** (92)
4	**1a** (H)	**2d** (4-Cl-C$_6$H$_4$, CN)	**3ad** (94)
5	**1a** (H)	**2e** (2-furan, CN)	**3ae** (71)
6	**1a** (H)	**2f** (2-thiophene, CN)	**3af** (82)
7	**1a** (H)	**2g** (Me, acetyl)	**3ag** (63)
8	**1a** (H)	**2h** (Ph, CO$_2$allylic)	**3ah** (56)
9	**1b** (Ph)	**2a** (Ph, CN)	**3ba** (56)
10	**1b** (Ph)	**2f** (2-thiophene, CN)	**3bf** (65)
11	**1c** (Bu)	**2a** (Ph, CN)	**3ca** (32)

[a] For reaction conditions, see Supporting Information. [b] Isolated yield.

(6) For recent examples, see: (a) Sun, J.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 4568. (b) Zhang, Q.; Yang, L.; Tong, X. *J. Am. Chem. Soc.* **2010**, *132*, 2550. (c) Smith, S. W.; Fu, G. C. *J. Am. Chem. Soc.* **2009**, *131*, 14231. (d) Xiao, H.; Chai, Z.; Zheng, C.-W.; Yang, Y.-Q.; Liu, W.; Zhang, J.-K.; Zhao, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 4467. (e) Wang, T.; Ye, S. *Org. Lett.* **2010**, *12*, 4168. (f) Xu, S.; Zhou, L.; Ma, R.; Song, H.; He, Z. *Org. Lett.* **2010**, *12*, 544. (g) Wang, Z.; Castellano, S.; Kinderman, S. S.; Argueta, C. E.; Beshir, A. B.; Fenteany, G.; Kwon, O. *Chem.—Eur. J.* **2010**, *17*, 649. (h) Zhang, X.-C.; Cao, S.-H.; Wei, Y.; Shi, M. *Org. Lett.* **2011**, *13*, 1142. (i) Han, X.; Wang, Y.; Zhong, F.; Lu, Y. *J. Am. Chem. Soc.* **2011**, *133*, 1726.

(7) For recent examples, see: (a) Cai, L.; Zhang, B.; Wu, G.; Song, H.; He, Z. *Chem. Commun.* **2011**, *47*, 1045. (b) Wang, D.-W.; Syu, S.; Hung, Y.-T.; Chen, P.; Lee, C.-J.; Chen, K.-W.; Chen, Y.-J.; Lin, W. *Org. Biomol. Chem.* **2011**, *9*, 363. (c) Zhong, F.; Wang, Y.; Han, X.; Huang, K.-W.; Lu, Y. *Org. Lett.* **2011**, *13*, 1310. (d) Jiang, Y.-Q.; Shi, Y.-L.; Shi, M. *J. Am. Chem. Soc.* **2008**, *130*, 7202. (e) Zhou, R.; Wang, J.; Song, H.; He, Z. *Org. Lett.* **2011**, *13*, 580. (f) Zheng, S.; Lu, X. *Org. Lett.* **2009**, *11*, 3978.

(8) For recent examples, see: (a) Wilson, J. E.; Sun, J.; Fu, G. C. *Angew. Chem., Int. Ed.* **2010**, *49*, 161. (b) Chung, Y. K.; Fu, G. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 2225. (c) Meng, L.-G.; Hu, B.; Wu, Q.-P.;

After establishing the optimized conditions (Tables S1−S2 in Supporting Information), we set out to investigate the scope of Type I annulations and the results are summarized in Table 1. In general, the reactions produce fully substituted furans **3** in medium to excellent yields from a wide arrange of substrates **2** with substituted phenyl groups, heteroaromatic rings, and alkyl groups. The electron-withdrawing group of substrates **2** imposes some effect on the results; the cyano affords the best results while the acyl and ester give lower yields probably due to their weaker electron-withdrawing effect. One limitation in the case of **1a**, however, is the unavoidable result of the C2 methyl in products **3**, which can be complemented by the use of γ-substituted substrate **1**, such as **1b** and **1c**, although the corresponding yields are somewhat lower (entries 9−11, Table 1).
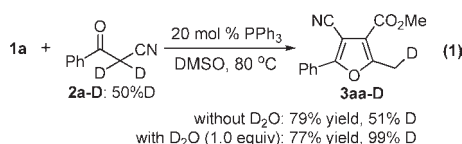
To better understand the mechanism of the Type I annulations, deuterium-labeled **2a-D** (50% D) was subjected to the same conditions. Compound **3aa** was obtained in a yield less than that of **2a** but with 51% D at its methyl group (eq 1). Interestingly, when the reaction of **1a** and **2a-D** was conducted in the presence of D$_2$O (1.0 equiv) under otherwise identical conditions, the deuterium rate was increased to 99% at the same carbon (eq 1). These results strongly indicated the formation of intermediate(s) featuring a carbanion located at the γ-carbon of butynoate **1a**.

On the basis of these observations, a reaction mechanism is proposed (Scheme 3). Addition of catalyst to **1a** generates zwitterionic intermediate **A-1**. In the presence of **2a**, **A-1** works as a base to initiate H-transfer, leading to the formation of intermediate **B-1** and a nucleophile.[11] Then, α-addition and elimination of acetate produce intermediate **C**, which is converted to intermediate **F** via double continuous steps of H-transfer and isomerization. The results of deuterium-labeling experiments strongly implied that the involved H-transfer occurs through both intramolecular and intermolecular pathways.[12] Finally, the addition−elimination process takes place to regenerate the catalyst and give product **3aa**.

Scheme 3. Proposed Mechanism for Type I Annulations
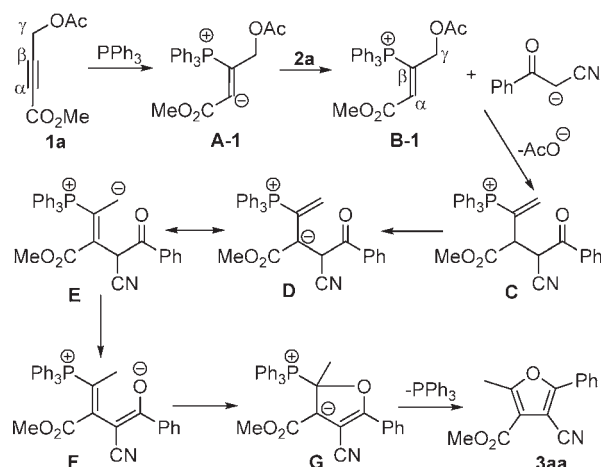
While α-addition is an overwhelming reactivity for intermediate **B-1**, we believe that the unique function of allylic acetate at its γ-carbon might also be available for S$_N$2-substitution. To access the feasibility of this postulation, substrates **1** with various leaving groups were explored, as well as several additives. To our delight, it was eventually identified that the reaction of **1d** with bromine as a leaving group and **2a** in the presence of 20 mol % PPh$_3$ with the assistance of Ag$_2$O exclusively afforded furan **4da** in 85% yield (entry 1, Table 2). Thus, Type II annulation was realized, which incorporated βC and γC of butynoate **1d** into a furan cycle. It was worth noting that, with the use of Cs$_2$CO$_3$ instead of Ag$_2$O, the reaction of **1d** and **2a** just gave compound **3aa** in 37% yield (entry 2, Table 2), demonstrating the crucial role of Ag$_2$O on regioselectivity. However, without PPh$_3$, only Ag$_2$O reagent could not promote any reactions between **1d** and **2a**, and both substrates were recovered, suggesting that Ag$_2$O did not work as a base in this transformation. The generality of Type II annulations was also investigated, and the results are shown in Table 2.

The proposed mechanism of Type II annulations is presented in Scheme 4. Apparently, the combination of a bromine leaving group and Ag$_2$O additive facilitates S$_N$2 substitution at the γ-carbon of intermediate **B-2**, switching the reaction pathway to yield intermediate **H**, which ultimately accomplished Type II annulations.

Lianga, M.; Xue, S. *Chem. Commun.* **2009**, 6089. (d) Sampath, M.; Loh, T.-P. *Chem. Sci.* **2010**, *1*, 739. (e) Liu, B.; Davis, R.; Joshi, B.; Reynolds, D. W. *J. Org. Chem.* **2002**, *67*, 4595. (f) Sriramurthy, V.; Barcan, G. A.; Kwon, O. *J. Am. Chem. Soc.* **2007**, *129*, 12928. (g) Sriramurthy, V.; Kwon, O. *Org. Lett.* **2010**, *12*, 1084. (h) Tejedor, D.; Santos-Expósito, A.; Méndez-Abt, G.; Ruiz-Pérez, C.; García-Tellado, F. *Synlett* **2009**, 1223. (i) Yavari, I.; Souri, S.; Sirouspour, M.; Djahaniani, H. *Synthesis* **2006**, 3243.

(9) Jung, C.-K.; Wang, J.-C.; Krische, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 4118.

(10) (a) Tejedor, D.; Lpez-Tosco, S.; Gonzlez-Platas, J.; Garca-Tellado, F. *Chem.—Eur. J.* **2009**, *15*, 838. (b) Maezaki, N.; Yagi, S.; Ohsawa, S.; Ohishib, H.; Tanaka, T. *Tetrahedron* **2003**, *59*, 9895.

(11) (a) Trost, B. M.; Li, C. J. *J. Am. Chem. Soc.* **1994**, *116*, 3167. (b) Trost, B. M.; C. Li, J. *J. Am. Chem. Soc.* **1994**, *116*, 10819. (c) Trost, B. M.; Dake, G. R. *J. Org. Chem.* **1997**, *62*, 5670. (d) Dake, G. R.; Trost, B. M. *J. Am. Chem. Soc.* **1997**, *119*, 7595. (e) Zhang, C.; Lu, X. *Synlett* **1995**, 645. (f) Alvarez-Ibarra, C.; Csaky, A. G.; delaOliva, C. G. *Tetrahedron Lett.* **1999**, *40*, 8465. (g) Liu, B.; Davis, R.; Joshi, B.; Reynolds, D. W. *J. Org. Chem.* **2002**, *67*, 4595. (h) Lu, C.; Lu, X. *Org. Lett.* **2002**, *4*, 4677.

(12) (a) Xia, Y.; Liang, Y.; Chen, Y.; Wang, M.; Jiao, L.; Huang, F.; Liu, S.; Li, Y.; Yu, Z.-X. *J. Am. Chem. Soc.* **2007**, *129*, 3470. (b) Mercier, E.; Fonovic, B.; Henry, C.; Kwon, O.; Dudding, T. *Tetrahedron Lett.* **2007**, *48*, 3617. (c) Liang, Y.; Liu, S.; Xia, Y.; Li, Y.; Yu, Z.-X. *Chem.—Eur. J.* **2008**, *14*, 4361.

(13) The compounds **4** and **5** were distinguished by comparison of authentic samples according to the following literatures: (a) Suhre, M. H.; Reif, M.; Kirsch, S. F. *Org. Lett.* **2005**, *7*, 3925. (b) Kadota, J.; Komori, S.; Fukumoto, Y.; Murai, S. *J. Org. Chem.* **1999**, *64*, 7523.

Table 2. Scope of Type II Annulations[a]
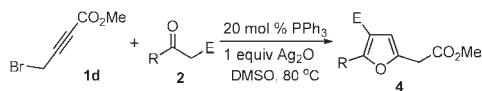
Entry	**2** (R, E)	**4** (yield %)[b]
1	**2a** (Ph, CN)	**4da** (85)
2	**2a** (Ph, CN)	**3aa** (37)[c]
3	**2b** (4-MeO-C_6H_4, CN)	**4db** (66)
4	**2c** (4-Br-C_6H_4, CN)	**4dc** (92)
5	**2d** (4-Cl-C_6H_4, CN)	**4dd** (96)
6	**2i** (4-NO_2-C_6H_4, CN)	**4di** (81)
7	**2e** (2-furan, CN)	**4de** (87)
8	**2f** (2-thiophene, CN)	**4df** (90)
9	**2g** (Me, acetyl)	**4dg** (63)
10	**2j** (cyclohexane-1,3-dione)	**4dj** (44)
11	**2k** (C_5H_{11}, CN)	**4dk** (75)
12	**2l** (diethyl 3-oxopentanedioate)	**4dl** (45)

[a] For reaction conditions, see Supporting Information. [b] Isolated yield. [c] Cs_2CO_3 was used instead of Ag_2O.

Scheme 4. Proposed Mechanism for Type II Annulations
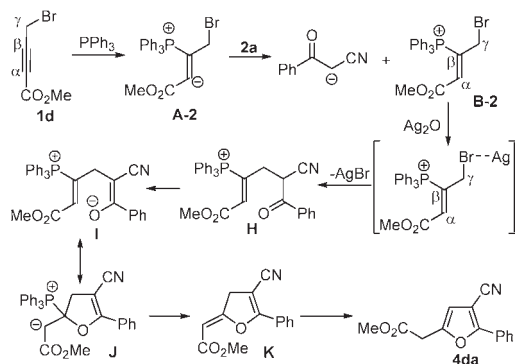
As expected, the reagent Cs_2CO_3 could promote β-addition of **2a** to **1a** in the absence of the PPh$_3$ catalyst, which was followed by γ-substitution and isomerization to furnish Type III annulation although the resulting new isomer[13] **5aa** was isolated only in 23% yield (entry 1, Table 3). Interestingly, substrate **1d** gave the same product but with a lower yield (entry 2, Table 3). When substrates **2g** and **2m** were used, the corresponding yields were increased to 59% and 73%, respectively, implying that β-addition strongly relied on the pK_a value of **2**. These

results indicated that the PPh$_3$ catalyst played a crucial role in regioselectivity possibly due to its stronger nucleophilicity than that of **2**, which would enable the β-position of **1** being preferentially occupied by PPh$_3$ over **2**.

Table 3. Scope of Type III Annulations[a]
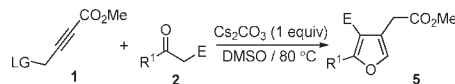
Entry	**1** (LG)	**2** (R^2, E)	**5** (yield %)[b]
1	**1a** (OAc)	**2a** (Ph, CN)	**5aa** (23)
2	**1d** (Br)	**2a** (Ph, CN)	**5aa** (18)
3	**1a** (OAc)	**2g** (Me, acetyl)	**5ag** (59)
4	**1a** (OAc)	**2m** (Me, CO_2Et)	**5am** (73)

[a] For reaction conditions, see Supporting Information. [b] Isolated yield.

In summary, we have developed [3 + 2] annulations between γ-functionalized butynoates **1** and 1C,3O-bisnucleophiles **2** in a reagent-controlled manner, leading to three distinct furan skeletons with high selectivity. The PPh$_3$ catalyst enables α-addition of **2** to **1** to be favorable, and fully substituted furans **3** are obtained in good to excellent yields. In the absence of the PPh$_3$ catalyst, a normal β-addition takes up the reactivity of **1a**, affording furan derivatives **5**. For butynoate **1d**, γ-substitution exclusively generates a third furan skeleton **4** with the combination of the PPh$_3$ catalyst and the reagent Ag_2O. The following facts may contribute to the high selectivity: (1) PPh$_3$ catalyst exhibits stronger affinity toward the β-position of butynoate **1** than that of 1C,3O-bisnucleophiles **2**, diminishing the competition from the addition of **2** to the β-position of **1**; (2) to form AgBr, precipitation might provide a powerful driving force to facilitate γ-substitution.

Supporting Information Available. Experimental procedures and copies of NMR spectra for all new products. This material is available free of charge via the Internet at http://pubs.acs.org.